(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 389 282 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
20.02.2002 Bulletin 2002/08

(51) Int Cl.[7]: **C07D 473/06**, A61K 31/52, A61P 25/28

(21) Application number: **90303093.0**

(22) Date of filing: **22.03.1990**

(54) Xanthinederivatives, process for their preparation and their pharmaceutical use

Xanthinderivate, Verfahren zu ihrer Herstellung und ihre pharmazeutische Anwendung

Dérivés de xanthine, procédé pour leur préparation et leur utilisation médicinale

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: **23.03.1989 GB 8906792**

(43) Date of publication of application:
26.09.1990 Bulletin 1990/39

(60) Divisional application:
00203905.5 / 1 120 417

(73) Proprietors:
- **SmithKline Beecham Pharma GmbH**
  80804 München (DE)
- **Beecham Group p.l.c.**
  Brentford, Middlesex TW8 9BD (GB)

(72) Inventors:
- **Maschler, Harald, c/o Beecham-Wuelfing**
  D-3212 Gonau (Leine) (DE)
- **Spicer, Barbara Ann, Beecham Pharmaceuticals**
  Epsom, Surrey KT 18 5XQ (GB)
- **Smith, Harry, Beecham Pharmaceuticals**
  Epsom, Surrey KT 18 5XQ (GB)

(74) Representative: **Rutter, Keith, Dr. et al**
SmithKline Beecham plc Corporate Intellectual Property, Two New Horizons Court
Brentford, Middlesex TW8 9EP (GB)

(56) References cited:
EP-A- 0 152 944
EP-A- 0 267 676
WO-A-86/06724

- **BIOCHEMISTRY, vol. 16, no. 15, 26th July 1977, pages 3316-3321, American Chemical Society, Washington, D.C., US; G. L. KRAMER et al.: "Selective Inhibition of cyclic nucleotide phosphodiesterases by analogues of 1-methyl-3-isobutylxanthine"**
- **JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 8, August 1981, pages 954-958, American Chemical Society, Washington, D.C., US; J. N. WELLS et al.: "Inhibition of separated forms of cyclic nucleotide phosphodiesterase from pig coronary arteries by 1,3-disubstituted and 1,3,8-trisubstituted xanthines"**

EP 0 389 282 B1

Description

[0001] The present invention relates to 8-amino xanthine derivatives having pharmacological activity, to a process for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

[0002] Molecular Pharmacology, Volume 6, No. 6, 1970, p.597-603 discloses 1,3-dimethyl-8-nitro-xanthine. This compound is disclosed as having lipolytic activity.

[0003] Annalen der Chemie, 47, 362-365 (1957) discloses 1,3- dimethyl-8-amino-xanthine and a process by which it may be prepared. No pharmacological utility is disclosed for this compound.

[0004] Drug Res. 27(1) Nr 19, 1977, pages 4-14, Van K.H. Klingler discloses certain 1,3-dimethyl- 8-substituted xanthines as intermediates solely in the synthesis of phenylethyl aminoalkyl xanthines.

[0005] Drug Res. 31 (11), Nr. 12, 1981, R.G. Werner et al, pages 2044-2048 discloses certain 1,3-dimethyl-8-substituted xanthines. No pharmacological activity is disclosed for these compounds.

[0006] Biochemistry, 16 (1977), 3316-3321 relates to certain analogues of 1-methyl-3-isobutylxanthine.

[0007] J.Med.Chem, 24 (1981), 954-958 relates to certain 1, 3-disubstituted and 1, 3, 8-trisubstituted xanthines.

[0008] WO-A-8606724 discloses substituted 2, 3-dihydro-6-hydroxy-pyrimido-[2, 1-f]-purine-4, 8, (1H, 9H)-diones and their use as anti-inflammatory and anti-allergy agents.

[0009] EP-A-0152944 discloses certain adenosine derivatives and their use as antiallergenics and bronchodilators.

[0010] EP-A-0267676 discloses the use of 1, 3-di-n-butyl-7-(2-oxypropyl) xanthine in the treatment of inter alia cerebrovasular disorders.

[0011] It has now been discovered that certain 8-substituted xanthines have a protective effect against the consequences of cerebral metabolic inhibition. The said compounds improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated with Parkinson's disease.

[0012] These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with the compound is indicated to be of benefit for the treatment of functional disorders resulting from disturbed brain function following ischaemia.

[0013] These compounds are also active in increasing the oxygen tension in ischaemic skeletal muscle. This property results in an increase in the nutritional blood flow through ischaemic skeletal muscle which in turn indicates that the compounds of the invention are of potential use as agents for the treatment of peripheral vascular disease such as intermittent claudication.

[0014] These compounds also act as phosphodiesterase inhibitors and elevate cyclic AMP levels and are therefore of potential use in the treatment of proliferative skin disease in human or non-human mammals.

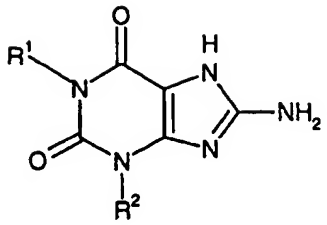
[0015] These compounds are also indicated to have bronchodilator activity and thus to be of potential use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

[0016] It has now also surprisingly been discovered that these compounds are good inhibitors of induced blood eosinophilia and that they are therefore potentially useful in the treatment and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

[0017] Certain of the novel compounds are also indicated to possess useful adenosine AI antagonist activity.

[0018] Finally the present compounds also show good metabolic stability.

[0019] Accordingly, the invention provides a compound of formula (IA):



(IA)

or if appropriate a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 each independently represents a moiety of formula (a):

$$-CH_2-A \qquad (a)$$

wherein A represents an unsubstituted single ring C_{3-8} cycloalkyl group.

[0020] In particular, A represents an unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

[0021] Favourably, A represents a cyclopropyl group or a cyclobutyl group.

[0022] Preferably, A represents a cyclopropyl group.

[0023] Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts.

[0024] The compounds of formula (IA) form acid addition salts, suitable acid addition salts of the compounds of formula (IA) are the acid addition salts including pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphate, α-keto glutarate, α-glycerophosphate and glucose-1-phosphate. Preferably the acid addition salt is a hydrochloride salt.

[0025] The pharmaceutically acceptable salts of the compounds of formula (IA) are prepared using conventional procedures.

[0026] When used herein the term 'cyclic hydrocarbon radical' includes single ring, cyclic hydrocarbons comprising up to 8 carbon atoms in the ring, suitably up to 6 carbon atoms, for example 3, 4, 5 or 6 carbon atoms.

[0027] When used herein the expression 'proliferative skin diseases' means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant keratosis, acne, and seborrheic dermatitis in humans and atopic dermatitis and mange in domesticated animals.

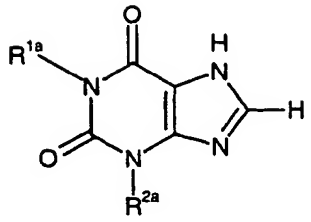
[0028] The compounds of formula (IA) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

[0029] In another aspect, the invention provides the use of a compound of formula (IA), or if appropriate a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin diseases and/or disorders of the respiratory tract and/or the treatment or prophylaxis of disorders associated with increased numbers of eosinophils and allergic disorders associated with atopy.

[0030] The present invention also provides a pharmaceutical composition comprising a compound of formula (IA) or if appropriate a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

[0031] In a further aspect the invention provides a compound of formula (IA), or if appropriate a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance.

[0032] The compounds of formula (IA) are prepared by reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1, as defined in relation to formula (IA), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (IA), or a group convertible thereto, with a reagent capable of substituting the C-8 hydrogen of the compound of formula (II) with a group R^{3b} wherein R^{3b} represents amino or a group convertible thereto; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2;
(ii) when R^{3b} is not amino, converting R^{3b} to amino;
(iii) converting a compound of formula (IA) into a further compound of formula (IA);
(iv) converting a compound of formula (IA) into a pharmaceutically acceptable salt.

[0033] One preferred group R^{3b} is a nitro group which may then be converted to amino.

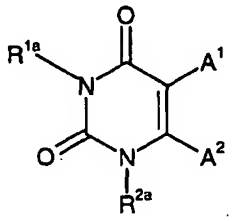
[0034] Suitable reagents for substituting the C-8 hydrogen of the compound of formula (II) with a group R^{3b} are the appropriate conventional reagents.

[0035] The conditions of reaction for the substitution of the C-8 hydrogen of the compound of formula (II) will of course depend upon the particular reagent chosen, and in general the conditions used will be those which are conventional for the reagent used.

[0036] One particularly suitable reagent is a nitrating agent.

[0037] In one convenient form of the abovementioned process the compound of formula (II) is reacted with a suitable nitrating agent to provide a compound of formula (IA) wherein R^{3a} represents a nitro group and then converting the nitro group into a halogen atom or an amino group.

[0038] A compound of formula (II) may be prepared by the dehydrating cyclisation of a compound of formula (III):



(III)

wherein R^{1a} represents R^1, as defined in relation to formula (IA), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (IA), or a group convertible thereto, A^1 represents - NO or -NH-CHO and A^2 represents $-NH.CH_3$ or $-NH_2$, providing that when A^1 is -NO then A^2 is $-NH.CH_3$ and when A^1 is -NH.CHO then A^2 is NH_2; and thereafter, if required, converting any group R^{1a} to R^1 and/or R^{2a} to R^2.

[0039] The dehydrating cyclisation of a compound of formula (III) may be carried out under any suitable conditions. Favourably the conditions chosen are these wherein the water formed is removed from the reaction mixture, thus the reaction is generally carried out at an elevated temperature in the range of from 100°C to 200°C, such as in the range of 180°C to 190°C.

[0040] In one aspect of the process, especially when A^1 is -NO and A^2 is $-NH.CH_3$, the reaction is carried out in a solvent immiscible with water, such as toluene, at the reflux temperature of the solvent, the water being removed using a water-separator.

[0041] Suitable values for R^{1a} and R^{2a} include R^1 and R^2 respectively or nitrogen protecting groups such as benzyl groups.

[0042] When R^{1a} or R^{2a} represents other than R^1 or R^2 repectively, the abovementioned conversions of R^{1a} into R^1 and R^{2a} to R^2 may be carried out using the appropriate conventional procedure. For example when R^{1a} (or R^{2a}) represents a nitrogen protecting group, such as a benzyl group, the protecting group may be removed using the appropriate conventional procedure, such as catalytic hydrogenation, and the resulting product reacted with a compound of formula (IV):

$$X\text{-}CH_2\text{-}A \qquad (IV)$$

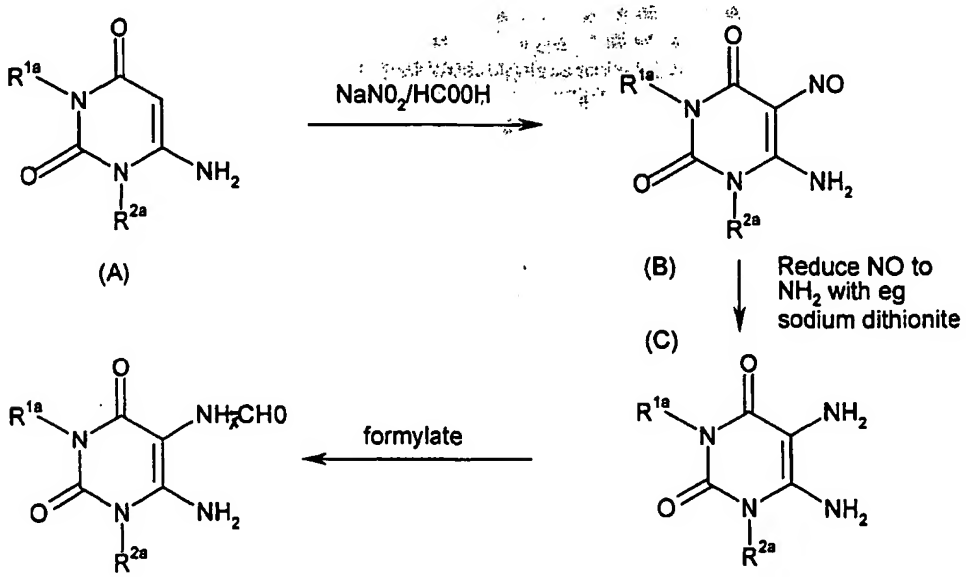
wherein A and is as defined in relation to formula (IA) and X represents a leaving group, such as halide, for example bromide or iodide.

[0043] The protection of any reactive group or atom, such as the xanthine nitrogen atom may be carried out at any appropriate stage in the aforementioned process. Suitable protecting groups include those used conventionally in the art for the particular group or atom being protected, for example suitable protecting groups for the xanthine nitrogen atoms are benzyl groups.

[0044] Protecting groups may be prepared and removed using the appropriate conventional procedure:

[0045] For example, N-benzyl protecting groups may be prepared by treating the appropriate compound of formula (II) with benzyl chloride in the presence of a base such as triethylamine. The N-benzyl protecting groups may be removed by catalytic hydrogenation over a suitable catalyst, such as palladium on activated charcoal, in a suitable solvent, such as ethanol conveniently at an elevated temperature, or by treatment with anhydrous aluminium chloride in dry benzene at ambient temperature.

[0046] A compound of formula (III) wherein A^1 represents -NH-CHO and R^2 represents $-NH_2$ may suitably be prepared from a 6-aminouracil of formula (A) according to the following reaction scheme:



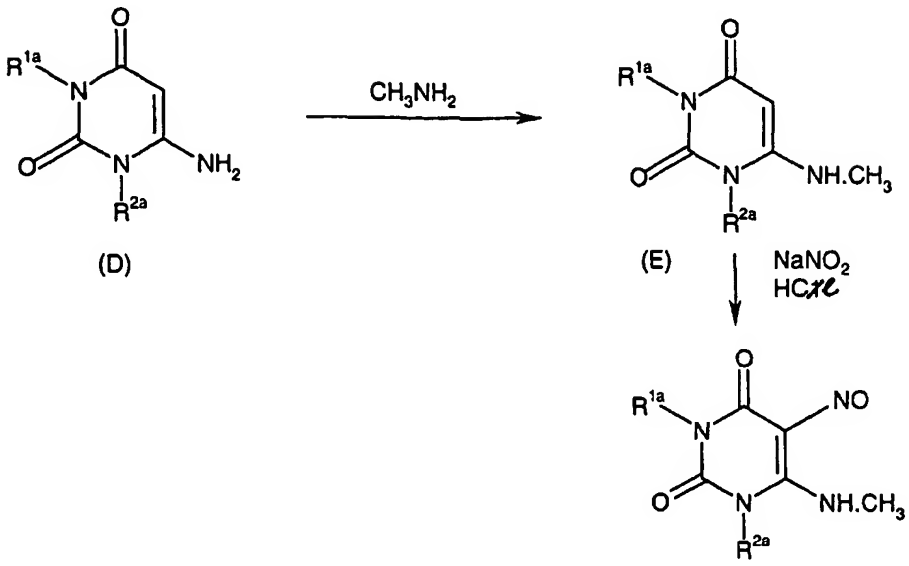
wherein R^{1a} and R^{2a} are as defined in relation to formula (II).

[0047] Suitably, the reaction conditions used in the abovementioned reaction scheme are appropriate conventional conditions. In a preferred aspect of the process, the conversion of the 6-aminouracil (A), via (B) and (C), to the corresponding compound of formula (III) and the cyclisation of the compound of formula (III) to the compound of formula (II) are all carried out in-situ, suitably by using an analogous procedure to that of H. Bredereck and A. Edenhofer, Chem. Berichte 88, 1306-1312 (1955).

[0048] The 6-aminouracils of formula (A) may themselves be prepared by the method of V. Papesch and E. F. Schroder, J. Org. Chem., 16, 1879-90 (1951), or Yozo Ohtsuka, Bull. Chem. Soc. Jap., 1973, 46(2), 506-9.

[0049] A compound of formula (III) wherein A^1 represents -NO and A^2 represents $-NH.CH_3$ may conveniently be

prepared from a 6-chlorouracil of formula (D), according to the following reaction scheme:



wherein R^{1a} and R^{2a} are as defined in relation to formula (II).

[0050] Suitably, the reaction conditions used in the last above mentioned scheme are the appropriate conventional conditions, for example those used in the method of H. Goldner, G. Dietz and E. Carstens, Liebigs Annalen der Chemie, 691, 142-158 (1965). The 6-chlorouracil of formula (D) may also be prepared according to the procedure of Dietz et al.

[0051] A nitro group may conveniently be converted into an amino group by conventional reduction methods for example by using tin powder and concentrated hydrochloric acid at ambient temperature or by using sodium dithionite in aqueous methanol at ambient temperature.

[0052] Suitable alkylation methods for use in the abovementioned conversions include those used conventionally in the art, for example methods using halides, preferably iodides, in the presence of a base such as potassium carbonate in any convenient solvent for example acetonitrile or toluene.

[0053] Suitable acylation methods for use in the abovementioned conversions include those used conventionally in the art, thus an amino group may be converted into an alkylcarbonyl amino group by using an appropriate acylating agent, for example an amino group may be converted to an acetylamino group by using acetic anhydride at elevated temperature.

[0054] The compounds of formula (IA) may be prepared according to the abovementioned methods or, as appropriate, by the methods of the abovementioned publications.

[0055] The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

[0056] The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

[0057] In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

[0058] Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

[0059] The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

[0060] Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

[0061] Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

[0062] Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; xanthine derivatives such as theophylline and aminophylline and corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

[0063] For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing.

[0064] Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

[0065] The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

[0066] Compounds of formula (IA), or if appropriate a pharmaceutically acceptable salt thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

[0067] Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

[0068] Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (IA) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

[0069] Suitably, the compound of formula (IA), or if appropriate a pharmaceutically acceptable salt thereof, will comprise from 0.5 to 20% by weight of the formulation, favourably from 1 to 10%, for example 2 to 5%.

[0070] The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000 mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day; and such therapy may extend for a number of weeks or months.

[0071] When used herein the term 'pharmaceutically acceptable' encompasses materials suitable for both human and veterinary use.

[0072] No toxicological effects have been established for the compounds of formula (IA) in the abovementioned dosage ranges.

[0073] The following pharmacological data and examples illustrate the invention. The following preparations illustrate the preparation of intermediates to the novel compounds of formula (IA).

Demonstration Example 1

1,3-Di-n-butyl-8-nitro xanthine

[0074] 1,3-Di-n-butylxanthine (73g, 0.28mol) was dissolved in acetic acid (120ml) and then treated with concentrated nitric acid (49g) at 87°C. After 1 hour, the mixture was cooled to 5°C, the resulting yellow precipitate filtered off and washed with water (50ml). The yellow crystals were dissolved in dichloromethane and washed twice with water. The separated organic layer was then dried (anhydrous sodium sulphate) and concentrated to give a crystalline product, yield 73g (86%), m.pt 168°C

^{1}H NMR ($CDCl_3$/DMSO):

ppm: 0.93 (t, J=6.3Hz, 6H), 1.1-2.0 (m, 8H), 3.8-4.25 (m, 4H).

Demonstration Example 2

1,3-Di-cyclopropylmethyl-8-nitro xanthine

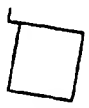
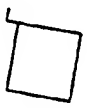
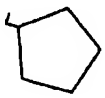
[0075] 1,3-Di-cyclopropylmethyl xanthine (20g, 0.076mol) was dissolved in acetic acid (33ml) and then treated with concentrated nitric acid (13.2g) at 87°C. After 1 hour, the mixture was cooled to 5°C and the resulting yellow precipitate filtered off. The yellow crystals were dissolved in dichloromethane and washed with water. The separated organic layer was then dried over anhydrous sodium sulphate and concentrated in vacuo. The product crystallized from the concentrate to yield a yellow crystalline product yield 12.2g, (56.5%), m.pt. 207°C (with decomposition).

^{1}H NMR ($CDCl_3$):

ppm: 0.35-0.7 (m, 8H), 1.1 -1.7 (m, 2H), 3.95-4.2 (m, 4H), 9.0-11.0 (br. exchanges with D_2O, 1H).

[0076] The following compounds were prepared using an analogous procedure to that described in Demonstration Example 1. The appropriate 1,3-di-cycloalkylmethyl xanthine substrates were prepared according to the procedures described herein in and in United Kingdom Patent Application No. 8826595.4.

Table 1

Demonstration Ex No	R^1	R^2	R^3	M.pt (°C)	^{1}H NMR Spectrum: ($CDCl_3$ or $CDCl_3$/DMSO, ppm)
3			NO_2	220	1.7-2.2 (m, 12H) 2.5-3.1 (m, 2H) 4.1-4.3 (m, 4H)
4			NO_2	148-150	1.1 -2.0 (m, 16H) 2.15-2.7 (m, 2H) 4.15 (d, J=7.7H_z, 4H)
5			NO_2	140	0.75-2.2 (m, 22H) 3.7 -4.1 (m, 4H)

Demonstration Example 7

1,3-Di-n-butyl-8-amino xanthine hydrochloride

[0077] 1,3-Di-n-butyl-8-nitro xanthine from Example 1 (8.5g) was suspended in concentrated hydrochloric acid (85ml) and then treated at room temperature with tin powder (14.5g) in small portions. After stirring for 10 minutes the yellow colour of the suspension disappeared. Thereafter the precipitate was filtered off and recrystallised twice from ethanol. The product formed colourless crystals, yield 5.5g (63%) m.pt>250°C

^{1}H NMR (DMSO):

ppm: 0.90 (t, J=6.1Hz, 6H), 1.05-1.9 (m, 8H), 3.65-4.15 (m, 4H), 6.9 (br, exchanges with D_2O, 4H).

Example 1

1,3-Di-cyclopropylmethyl-8-amino xanthine

[0078] 1,3-Di-cylopropylmethyl-8-nitro xanthine (4g, 0,014mol), suspended in 50ml of concentrated hydrochloric acid,was treated with small portions of tin (8g) at room temperature. The mixture was then stirred at room temperature for two hours.

[0079] The resulting precipitate was filtered off and crystallised from ethanol to give white crystals of the title product, yield 0.9g (23%), m.pt. 281°C.

[0080] In an alternative procedure, using sodium dithionite as reducing agent (in methanol-water mixture). The yield was 36% (compare Demonstration Example 8).

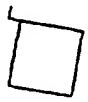
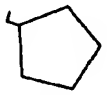
^{1}H NMR ($CDCl_3$):

ppm: 0.3-0.6 (m,8H), 1.0-1.6 (m,2H), 3.7-4.0 (m,4H), 5.75 (br,2H), 10.84 (br. exchanges with D_2O, 1H).

Examples 2 to 4

[0081] The following compounds were prepared using an analogous procedure to that described above for the preparation of a compound of Demonstration Example 1.

Table 2

Ex No	R^1	R^2	R^3	M.pt (°C)	^{1}H NMR Spectrum: ($CDCl_3$ or $CDCl_3$/DMSO, ppm)
2			NH_2	124 (decomp)	1.65-2.2 (m, 12H) 2.5-3.1 (m, 2H) 3.85-4.2 (m, 4H) 6.5-8.5 (br, 4H
3			NH_2	300	1 -1.9 (m, 16H) 2.15-2.7 (m, 2H) 3.65-4.0 (m, 4H) 6.45 (br, 2H) 11.20 (br, 1H)
4			NH_2	300	0.7-2.2 (m, 22H) 3.65-3.95 (m, 4H) 6.51 (s, 2H) 10-13 (br, 1H)

Preparation 1

1,3-Di-cyclopropylmethyl xanthine

[0082] 1,3-Di-cyclopropylmethyl xanthine was prepared using an analogous procedure to that described in Chem. Berichte 88, 1306-1312, 1955: 20.2g (0.0855 mol) of 1,3-dicyclopropylmethyl-6-amino-uracil was dissolved in 100ml of formamide, then 5.9g sodium nitrite was added and at 60°C 13.4ml formic acid was added slowly with stirring. After the colour had changed from yellow to violet, the mixture was heated up to 100°C and 3.1g of sodium dithionite ($Na_2S_2O_4$) was added in small portions.

[0083] Then the mixture was heated to 180-190°C and held at this temperature for 30 minutes.

[0084] After cooling, the precipitate was sucked off, washed with 50ml of water and recrystallised from toluene. Yield: 22.5g, m.p. 203°C.

^{1}H NMR ($CDCl_3$):

ppm: 0.44-0.54 (8H, q); 1.18-1.57 (2H, m); 3.98-4.12 (4H, 2d); 7.81 (1H, s); 12.8-13.2 (1H, s, exch. with D_2O).

Preparation 2

1,3-Di-cyclobutylmethyl xanthine

[0085] 1,3-Di-cyclobutylmethyl xanthine was prepared from 1,3-dicyclobutylmethyl-6-aminouracil using an analogous procedure to that described in Preparation 1. The title compound was isolated as a crystalline solid, m.p. 191°C.
^{1}H NMR ($CDCl_3$):
ppm: 1.6-2.3 (12H, m); 2.4-3.2 (2H, m); 4.16 (2H, d, J=7.0Hz); 4.21 (2H, d, J=7.3Hz); 7.76 (1H, d, J=1.3Hz, exch. with D_2O to give s) 12.7 (1H, br.s, exch. with D_2O).

Preparation 3

1,3-Di-cyclopentylmethyl xanthine

[0086] 1,3-Di-cyclopentylmethyl xanthine was prepared from 1,3-di-cyclopentylmethyl-6-aminouracil using an analogous procedure to that described in Preparation 1. The title compound was isolated as a crystalline solid, m.p. 208°C.
^{1}H NMR ($CDCl_3$):
ppm: 1.0-2.0 (16H, m); 2.2-2.9 (2H, m); 4.0-4.3 (4H, m); 7.78 (1H, d, J=1.2Hz, exch. with D_2O to give s; 12.9 (1H, br. s, exch. with D_2O).

Preparation 4

1,3-Di-cyclohexylmethyl xanthine

[0087] 1,3-Di-cyclohexylmethyl xanthine was prepared from 1,3-di-cyclohexylmethyl-6-aminouracil using an analogous procedure to that described in Preparation 1. The title compound was isolated as a crystalline solid,m.p. 237°C.
^{1}H NMR ($CDCl_3$):
ppm: 0.8-2.2 (22H, m); 3.85-4.15 (4H, m (dd)); 7.73 (1H, s); 13.1 (1H, br.s, exch. with D_2O).

Preparation 5

1,3-Di-cyclopropylmethyl-6-aminouracil

[0088] 1,3-Di-cyclopropylmethyl-6-aminouracil was prepared using an analogous procedure to that described in J. Org. Chem. 16, 1879-1890, (1951):
[0089] 22.6g (0.138mol) of the N,N'-dicyclopropylmethyl-urea (from Preparation 1) was treated with 44ml (0.43mol) of acetic anhydride and 14g (0.165mol) of cyanocetic-acid at 70°C for 2 hours.
[0090] After cooling and the addition of 15ml of water, 40ml of 50% NaOH/water-solution was dropped slowly onto the mixture at 45°C with stirring.
[0091] After stirring for 1 hour at room temperature, the strongly alkaline solution was separated and the oily residue washed carefully with 60ml water.
[0092] The semi-solid residue was dissolved in 220ml methanol and dropped into 1 litre of water with stirring. Thereby the product crystallised. Yield: 25.5g, 78.5% approx., m.p. 85-95°C (wax-like).

Preparation 6

1,3-Di-cyclopentylmethyl-6-aminouracil

[0093] 1,3-Di-cyclopentylmethyl-6-aminouracil was prepared from N,N'-di-cyclopentylmethyl urea using a procedure analogous to that described in Preparation 5. The title compound was isolated as a crystalline solid, m.p. 108°C.
^{1}H NMR ($CDCl_3$):
ppm: 1.0-2.6 (18H, m); 3.86 (4H, d, J = 7.4H_z); 4.98 (3H, m, 2H exch. with D_2O).

Preparation 7

1,3-Di-cyclohexylmethyl-6-aminouracil

[0094] 1,3-Di-cyclohexylmethyl-6-aminouracil was prepared from N,N'-di-cyclohexylmethyl urea using a procedure

analogous to that described in Preparation 5. The title compound was isolated as a crystalline solid, m.p. 185°C.

Preparation 8

N,N'-Di-cyclopropylmethyl urea

[0095] N,N'-Di-cyclopropylmethyl urea, m.p. 124°C, was prepared using a procedure analogous to that described in J. Org. Chem. 16, 1879-1890, (1951):

[0096] 68.2g (0.634mol) cyclopropylmethylamine-hydrochloride in 800ml of water was treated with 25g sodium hydroxide dissolved in 100ml of water and the mixture cooled to -15°C.

[0097] Phosgene, 33g was then slowly introduced through a capillary tube with stirring. Thereafter the mixture was stirred for 1 hour and, as necessary, after acidification with 0.1 N HCl, the product was extracted with dichloromethane.

[0098] After washing with water and drying over anhydrous sodium sulphate the product was obtained after evaporation of the solvent. Yield: 21g, 40% approx.

[0099] From the aqueous phase, 20g of the unreacted aduct (cyclopropylmethylamine-hydrochloride) can be obtained.

^{1}H NMR ($CDCl_3$):
ppm: 0.06-0.59 (8H, m); 0.72-1.06 (2H, m); 3.01-3.09 (4H, d); 4.66 (1H, br.s, exch. with D_2O).

Preparation 9

N N'-Di-cyclobutylmethyl urea

[0100] N,N'-Di-cyclobutylmethyl urea was prepared from cyclobutylmethylamine using a procedure analogous to that described in Preparation 8. The title compound was isolated as a crystalline solid, m.p. 155°C.

^{1}H NMR ($CDCl_3$):
ppm: 1.4-2.8 (14H, m); 3.0-3.3 (4H, m); 4.59 (2H, br.s, exch. with D_2O).

Preparation 10

N,N'-Di-cyclopentylmethyl urea

[0101] N,N'-Di-cyclopentylmethyl urea was prepared from cyclopentylmethylamine using a procedure analogous to that described in Preparation 8. The title compound was isolated as a crystalline solid, m.p. 150°C.

^{1}H NMR ($CDCl_3$):
ppm: 1.0-2.2 (18H, m); 2.9-3.2 (4H, m); 4.59 (2H, br.s, exch. with D_2O).

Preparation 11

N N'-Di-cyclohexylmethyl urea

[0102] N,N'-Di-cyclohexylmethyl urea was prepared from cyclohexylmethylamine using a procedure analogous to that described in Preparation 8. The title compound was isolated as a crystalline solid, m.p. 159°C.

PHARMACOLOGICAL DATA

a) Inhibition of Cyclic AMP Phosphodiesterase

Procedure

[0103] The procedure used was that described by Arch, J.R.S. and Newsholme, E.A. in Biochem. J. 158, 603, (1976):

[0104] Erythrocytes were obtained from Na-citrate (16 mM; 0.1 ml/ml blood) anticoagulated blood by repeated centrifugation with removal of the buff coat and washing with an isotonic buffer (composition in mM: NaCl 13.7, KCl 4, $CaCl_2.2\,H_2O$ 1.8, $Na_2HPO_4.12\,H_2O$ 0.8, NaH_2PO_4 0.2, $MgSO_4.7\,H_2O$ 0.7, Hepes 3.4; pH 7.4).

[0105] The phosphodiesterase was extracted by mixing the erythrocytes with 4 volumes of 7 mM phosphate buffer, pH7.4, followed by sonification (3 x 10 sec; 100 W) and then centrifuging for 30 min at 4200 x g.

[0106] All supernatants were diluted in the extraction medium and assayed for phosphodiesterase activity within 6 hours of preparation, using the radiochemical procedure described in the above mentioned reference.

Results	
Example No.	Ki [μM] c-AMP phosphodiesterase (erythrocytes)
1	1.6
2	0.53
3	0.57

b) Induction of blood eosinophilia and the effects of drugs.

Animals

[0107] Male Charles River Sprague Dawley rats weighing between 250 to 300g were used.

[0108] The method used was a modification of that described by Laycock et al (Int. Arch. Appl. Immunol, (1986). 81, 363).

[0109] Sephadex G200, particle size 40 to 120 micron, was suspended in isotonic saline at 0.5mg/ml, and stored for 48h at 4°C. 1ml of the suspension was given intravenously to rats on days 0,2 and 5. A control group received saline. The test compound was given before the Sephadex on each occasion, with a contact time expected to give maximum activity at the time of the Sephadex administration. Blood was taken from the tail vein of the rats on day 7 for the determination of total and differential leucocyte counts.

[0110] A control group of at least 6 animals was included each time a compound was evaluated. The control group received Sephadex and the vehicle without test compound. The results in the drug treated animals were compared with the control group. Alternatively, if the mean for the control group for any experiment was not statistically different from the mean of the sum of all of the control groups, then the treated animal results for that experiment were compared with the mean of the sum of all the control groups.

Total and differential leucocyte counts.

[0111] 20μl samples of blood, taken from the tail vein of the rats, were added to 10ml of Isoton II and, within 30min, Zaponin (3 drops) was added, to lyse the erythrocytes. Five minutes later the total cell count was determined using a Coulter Counter Model DN. Differential leucocyte counts were carried out by fixing and staining a blood smear on a microscopic slide with May-Grunwald and Giemsa stains. A minimum of 400 cells were counted on each slide.

Statistics

[0112] Probability values were calculated using the Student's t test.

Results

[0113] The effect of the test compound upon Sephadex induced eosinophilia in the rat is set out in Table 3. The test compound was given orally 30 minutes before each injection of Sephadex. The results indicate that the test compound inhibits the induced eosinophilia in a dose dependent manner.

Table 3

Test Compound	Dose mg/kg (orally - 30 mins)	% of Control Mean ± SEM (n=12 or more)
Vehicle dosed control + sephadex I.v	-	100 ± 7
Negative control saline I.v.	-	10 ± 0.9***
Example 1	2.0	48 ± 7***
	0.2	61 ± 8**

Notes
** $p < 0.01$
*** $p < 0.001$

Table 3 (continued)

Test Compound	Dose mg/kg (orally - 30 mins)	% of Control Mean ± SEM (n=12 or more)
Example 2	5.0	47 ± 4***

*** p< 0.001

c) Adenosine Receptor Ligand Binding Assays

Procedure

[0114] The A_1, [^{3}H]-CHA binding assay was performed as described by Bruns et al in Mol. Pharm. 29, 331-346 (1986).

Test animals: Wistar rats ca. 250g.

[0115] Brains were removed and one gram of the relevant tissues (whole brain minus cerebellum for the [^{3}H]-CHA) were homogenized in 50mM Tris-HCl (pH 7.4) supplemented with 10µm PMSF (phenylmethanesulphonylfluoride)for 30 seconds with a Potter S homogenizer, 10 strokes at 1.500 r.p.m. The homogenate was diluted and centrifuged at 42000g for 18 minutes. The pellet was re-suspended with the Potter S homogenizer in Tris-HCl buffer and the centrifugation step repeated. The pellet was then resuspended in Tris-HCl buffer, which contained 1mM EDTA, and stored in plastic vials in liquid nitrogen. The membranes were used within one week.

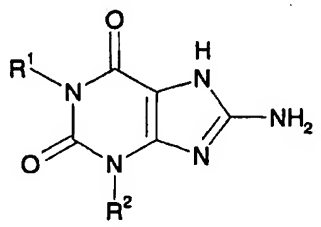
[0116] All incubations were performed in triplicate in 12 x 75mm polycarbonate tubes in a shaking water bath. Tubes contained 1ml of 50mM Tris-HCl (pH 7.4) and 2.5 or 0.1 units ml^{-1} of adenosine deaminase. Membranes obtained from 2mg of tissue in 400µl buffer were used in the [^{3}H]-CHA assay. The radiolabelled ligand concentrations were 2.5nm [^{3}H]-CHA. Non-specific binding was determined by the addition of 50µm PIA.

[0117] Incubations were for 90 minutes at 37°C for the [^{3}H]-CHA assay. Incubations were terminated by the addition of 3.8ml ice cold buffer (50mM Tris-HCl, 10mM $MgCl_2$; pH 7.4) followed by rapid filtration through 2.4cm GF/B filters under reduced pressure using a Millipore 1225 sampling manifold. Filters were washed with three 3.8ml portions of buffer. The damp filters were placed in scintillation vials and 5 ml of Aqualuma added. The vials were left overnight, shaken and radioactivity counted in a liquid scintillation counter. All assays were repeated at least three times.

Results	
Example No.	Adenosine A_1 inhibition Ki[µM]
1	5
2	7.2
3	4.6

Claims

1. A compound of formula (IA):



(IA)

or if appropriate a pharmaceutically acceptable salt thereof,
characterised in that:
R^1 and R^2 each independently represent a moiety of formula (a):

$-CH_2-A$ (a)

wherein A represents an unsubstituted single ring C_{3-8} cycloalkyl group.

2. A compound according to claim 1, wherein A is an unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

3. A compound according to claim1 or claim 2, wherein A represents a cyclopropyl group or a cyclobutyl group.

4. A compound according to any one of claims 1 to 3, wherein A represents a cyclopropyl group.

5. A compound according to claim 1 selected from the group consisting of:

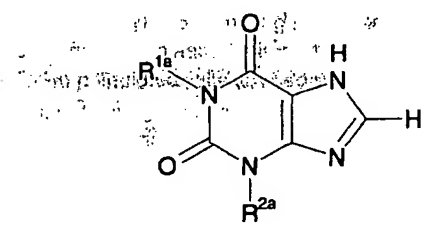
1,3-di-cyclopropylmethyl-8-amino xanthine;

1,3-di-cyclobutylmethyl-8-amino xanthine;

1,3-di-cyclopentylmethyl-8-amino xanthine;and

1,3-di-cyclohexylmethyl-8-amino xanthine; or if appropriate a pharmaceutically acceptable salt thereof.

6. A process for the preparation of a compound of formula (IA) according to claim 1, **characterised in that** the process comprises reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1, as defined in relation to formula (IA), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (IA), or a group convertible thereto, with a nitrating agent thereby substituting the C-8 hydrogen of the compound of formula (II) with a nitro group and thereafter converting the nitro group into an amine; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2;
(ii) converting a compound of formula (IA) into a pharmaceutically acceptable salt.

7. A pharmaceutical composition comprising a compound of formula (IA) according to claim 1, or-if appropriate a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

8. A compound of formula (IA) according to claim 1, or if appropriate a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance.

9. The use of a compound of formula (IA) according to claim 1 for the manufacture of a medicament for the treatment of cerebrovascular disorders and/or disorders associated with cerebral senility and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events and/or peripheral vascular disease and/or proliferative skin diseases and/or disorders of the respiratory tract and/or the treatment or prophylaxis of disorders associated with increased numbers of eosinophils and allergic disorders associated with atopy.

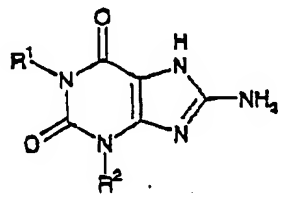
10. A compound according to claim 1 being

1,3-di-cyclopropylmethyl-8-amino xanthine; or if appropriate a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to claim 10.

Patentansprüche

1. Verbindung der Formel (IA):



(IA)

oder, falls zweckmäßig, ein pharmazeutisch verträgliches Salz davon,
dadurch gekennzeichnet, daß:
R^1 und R^2 jeweils unabhängig eine Einheit der Formel (a) darstellen:

$$-CH_2\text{-}A \qquad (a)$$

in der A einen unsubstituierten C_{3-8}-Cycloalkylrest mit einem einzigen Ring bedeutet.

2. Verbindung nach Anspruch 1, wobei A eine unsubstituierte Cyclopropyl-, Cyclobutyl-, Cyclopentyl- oder Cyclohexylgruppe ist.

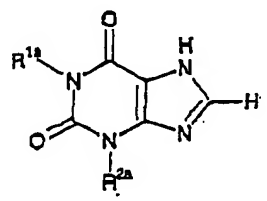
3. Verbindung nach Anspruch 1 oder Anspruch 2, wobei A eine Cyclopropyl- oder eine Cyclobutylgruppe bedeutet.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei A eine Cyclopropylgruppe bedeutet.

5. Verbindung nach Anspruch 1, ausgewählt aus:

1,3-Dicyclopropylmethyl-8-aminoxanthin;
1,3-Dicyclobutylmethyl-8-aminoxanthin;
1,3-Dicyclopentylmethyl-8-aminoxanthin; und
1,3-Dicyclohexylmethyl-8-aminoxanthin; oder, falls zweckmäßig, einem pharmazeutisch verträglichen Salz davon.

6. Verfahren zur Herstellung einer Verbindung der Formel (IA) nach Anspruch 1, **dadurch gekennzeichnet, daß** das Verfahren das Umsetzen einer Verbindung der Formel (II):



(II)

in der R^{1a} für R^1, wie mit Bezug auf Formel (IA) definiert, oder einen in R^1 umwandelbaren Rest steht, und R^{2a} für R^2, wie mit Bezug auf Formel (IA) definiert, oder einen dazu umwandelbaren Rest steht, mit einem Nitrierungs-

mittel, wodurch das C_8-Wasserstoffatom der Verbindung der Formel (II) durch eine Nitrogruppe substituiert wird und die Nitrogruppe anschließend in ein Amin umgewandelt wird; und, falls erforderlich, das anschließende Durchführen mindestens eines der folgenden fakultativen Schritte umfaßt:

(i) Umwandeln eines Rests R^{1a} in R^1 und/oder eines Rests R^{2a} in R^2;
(ii) Überführen einer Verbindung der Formel (IA) in ein pharmazeutisch verträgliches Salz.

7. Arzneimittel umfassend eine Verbindung der Formel (IA) nach Anspruch 1 oder, falls zweckmäßig, ein pharmazeutisch verträgliches Salz davon und einen pharmazeutisch verträglichen Träger dafür.

8. Verbindung der Formel (IA) nach Anspruch 1 oder, falls zweckmäßig, ein pharmazeutisch verträgliches Salz davon zur Verwendung als therapeutischen Wirkstoff.

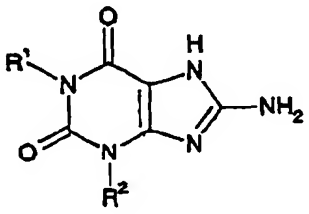
9. Verwendung einer Verbindung der Formel (IA) nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung von zerebrovaskulären Erkrankungen und/oder mit zerebraler Seniljtät verbundenen Erkrankungen und/oder Prophylaxe von Störungen, die mit aus ischämischen Vorfällen resultierender neuronaler Degeneration verbunden sind, und/oder peripherer Verschlußkrankheit und/oder wuchernden Hautkrankheiten und/oder Erkrankungen der Atemwege und/oder zur Behandlung oder Prophylaxe von mit einer erhöhten Anzahl von Eosinophilen verbundenen Störungen und mit Atopie verbundenen allergischen Leiden.

10. Verbindung nach Anspruch 1, bei welcher es sich um 1,3-Dicyclopropylmethyl-8-aminoxanthin handelt; oder, falls zweckmäßig, ein pharmazeutisch verträgliches Salz davon.

11. Arzneimittel umfassend eine Verbindung nach Anspruch 10.

Revendications

1. Composé de formule (IA) :



(IA)

ou, si cela est approprié, un de ses - sels pharmaceutiquement acceptables,
caractérisé en ce que :
R^1 et R^2 représentent chacun, indépendamment, un groupement de formule (a) :

$$-CH_2-A \qquad (a)$$

dans laquelle A représente un groupe cycloalkyle en C_3 à C_8 à un seul noyau, non substitué.

2. Composé suivant la revendication 1, dans lequel A représente un groupe cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexyle non substitué.

3. Composé suivant la revendication 1 ou la revendication 2, dans lequel A représente un groupe cyclopropyle ou un groupe cyclobutyle.

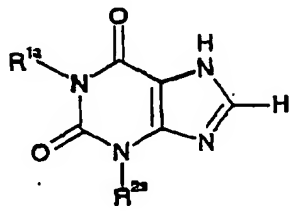
4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel A représente un groupe cyclopropyle.

5. Composé suivant la revendication 1, choisi dans le groupe consistant en les suivants :

1,3-di-cyclopropylméthyl-8-aminoxanthine ;
1,3-di-cyclobutylméthyl-8-aminoxanthine
1,3-di-cyclopentylméthyl-8-aminoxanthine; et
1,3-di-cyclohexylméthyl-8-aminoxanthine ; ou, si cela est approprié, un de ses sels pharmaceutiquement acceptables.

6. Procédé pour la préparation d'un composé de formule (IA) suivant la revendication 1, **caractérisé en ce qu'**il comprend la réaction d'un composé de formule (II) :

(II)



dans laquelle R^{1a} représente un groupe R^1, répondant à la définition mentionnée en rapport avec la formule (IA), ou un groupe pouvant être converti en un groupe R^1, et R^{2a} représente un groupe R^2, répondant à la définition mentionnée en rapport avec la formule (IA), ou un groupe pouvant être converti en un groupe R^2, avec un agent de nitration, en substituant ainsi l'atome d'hydrogène C-8 du composé de formule (II) par un groupe nitro, puis la conversion du groupe nitro en une amine ; et ensuite, si cela est requis, la mise en oeuvre d'une ou plusieurs des étapes facultatives suivantes :

(i) conversion de n'importe quel groupe R^{1a} en un groupe R^1 et/ou de n'importe quel groupe R^{2a} en un groupe R^2 ;
(ii) conversion d'un composé de formule (IA) en un sel pharmaceutiquement acceptable.

7. Composition pharmaceutique comprenant un composé de formule (IA) suivant la revendication 1 ou, si cela est approprié, un de ses sels pharmaceutiquement acceptables, et un support pharmaceutiquement acceptable à cette fin.

8. Composé de formule (IA) suivant la revendication 1 ou, si cela est approprié, un de ses sels pharmaceutiquement acceptables, destiné à être utilisé comme substance thérapeutique active.

9. Utilisation d'un composé de formule (IA) suivant la revendication 1 pour la production d'un médicament destiné au traitement de troubles vasculaires cérébraux et/ou de troubles associés à la sénilité cérébrale et/ou pour la prophylaxie de troubles associés à la dégénérescence des neurones résultant d'événements ischémiques et/ou d'une maladie vasculaire périphérique et/ou de maladies cutanées prolifératives et/ou de troubles du tractus respiratoire et/ou pour le traitement ou la prophylaxie de troubles associés à des nombres accrus de cellules éosinophiles et de troubles allergiques associés à une atopie.

10. Composé suivant la revendication 1, consistant en la 1,3-di-cyclopropylméthyl-8-aminoxanthine ou, si cela est approprié, un de ses sels pharmaceutiquement acceptables.

11. Composition pharmaceutique comprenant un composé suivant la revendication 10.